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LOGINID:SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS	4	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS	5	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS	6	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS	7	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	8	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	9	MAR 22	EMBASE is now updated on a daily basis
NEWS	10	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS	11	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS	12	APR 04	STN AnaVist \$500 visualization usage credit offered
NEWS	13	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS	14	APR 12	Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS	15	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS	16	MAY 10	CA/CAPLUS enhanced with 1900-1906 U.S. patent records
NEWS	17	MAY 11	KOREAPAT updates resume
NEWS	18	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS	19	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAPLUS and USPATFULL/USPAT2
NEWS	20	MAY 30	The F-Term thesaurus is now available in CA/CAPLUS
NEWS	21	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS EXPRESS			FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT <a href="http://download.cas.org/express/v8.0-Discover/">http://download.cas.org/express/v8.0-Discover/</a>
NEWS HOURS			STN Operating Hours Plus Help Desk Availability
NEWS LOGIN			Welcome Banner and News Items
NEWS IPC8			For general information regarding STN implementation of IPC 8
NEWS X25			X.25 communication option no longer available after June 2006

Enter NEWS followed by the item number or name to see news on that specific topic.

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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006

=> file reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0

DICTIONARY FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> E "RM2"/CN 25

E1	1	RM-ACID/CN
E2	1	RM189/CN
E3	0 -->	RM2/CN
E4	1	RM38/CN
E5	1	RM60 HOMOPOLYMER/CN
E6	1	RM7/CN
E7	1	RM711/CN
E8	1	RM715/CN
E9	1	RM721/CN
E10	1	RM723/CN
E11	1	RM80/CN
E12	1	RM801FW/CN
E13	2	RMA 1/CN
E14	1	RMA 1 (FLUX)/CN
E15	1	RMA 1 (RUBBER)/CN
E16	1	RMA 101/CN
E17	1	RMA 150M/CN
E18	1	RMA 1X/CN
E19	1	RMA 2/CN

E20	1	RMA 300M/CN
E21	1	RMA 325/CN
E22	1	RMA 390DH3/CN
E23	1	RMA 4/CN
E24	1	RMA 400/CN
E25	1	RMA 450M/CN

=> E "RM-2"/CN 25

E1	1	RM LUTE/CN
E2	1	RM PROTEIN (BACILLUS THURINGIENSIS ENTOMOCIDUS STRAIN LBIT-113 PLASMID PUIBI-1)/CN
E3	0 -->	RM-2/CN
E4	1	RM-ACID/CN
E5	1	RM189/CN
E6	1	RM38/CN
E7	1	RM60 HOMOPOLYMER/CN
E8	1	RM7/CN
E9	1	RM711/CN
E10	1	RM715/CN
E11	1	RM721/CN
E12	1	RM723/CN
E13	1	RM80/CN
E14	1	RM801FW/CN
E15	2	RMA 1/CN
E16	1	RMA 1 (FLUX)/CN
E17	1	RMA 1 (RUBBER)/CN
E18	1	RMA 101/CN
E19	1	RMA 150M/CN
E20	1	RMA 1X/CN
E21	1	RMA 2/CN
E22	1	RMA 300M/CN
E23	1	RMA 325/CN
E24	1	RMA 390DH3/CN
E25	1	RMA 4/CN

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

ENTRY

TOTAL

SESSION

FULL ESTIMATED COST

0.44

0.65

FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006

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FILE COVERS 1907 - 13 Jun 2006 VOL 144 ISS 25

FILE LAST UPDATED: 12 Jun 2006 (20060612/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/infopolicy.html>

=> s us 20050221397/pn

L1 1 US 20050221397/PN  
(US2005221397/PN)

=> sel rn  
E1 THROUGH E1 ASSIGNED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.49	3.14

FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
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STRUCTURE FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0  
DICTIONARY FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS  
for details.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of  
experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> s el  
L2 1 850223-38-0/BI  
(850223-38-0/RN)

=> d ibib  
'IBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual  
fields or predefined formats. The predefined substance formats  
are: (RN = CAS Registry Number)

REG	- RN
SAM	- Index Name, MF, and structure - no RN
FIDE	- All substance data, except sequence data
IDE	- FIDE, but only 50 names

SQIDE - IDE, plus sequence data  
 SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used  
 SQD - Protein sequence data, includes RN  
 SQD3 - Same as SQD, but 3-letter amino acid codes are used  
 SQN - Protein sequence name information, includes RN  
  
 CALC - Table of calculated properties  
 EPROP - Table of experimental properties  
 PROP - EPROP and CALC

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ABS -- Abstract  
 APPS -- Application and Priority Information  
 BIB -- CA Accession Number, plus Bibliographic Data  
 CAN -- CA Accession Number  
 CBIB -- CA Accession Number, plus Bibliographic Data (compressed)  
 IND -- Index Data  
 IPC -- International Patent Classification  
 PATS -- PI, SO  
 STD -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels  
 IBIB -- BIB, indented, with text labels  
 ISTD -- STD format, indented

OBIB ----- AN, plus Bibliographic Data (original)  
 OIBIB ----- OBIB, indented with text labels

SBIB ----- BIB, no citations  
 SIBIB ----- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.

The MAX format is the same as ALL.

The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.  
 HELP FORMATS -- To see detailed descriptions of the predefined formats.  
 ENTER DISPLAY FORMAT (IDE):end

=> d 1

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN  
 RN 850223-38-0 REGISTRY  
 ED Entered STN: 11 May 2005  
 CN  $\beta$ -D-Galactopyranose, O-2-(acetylamino)-2-deoxy- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-O-[N-acetyl- $\alpha$ -neuraminosyl-(2 $\rightarrow$ 3)]-O- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 3)-O-[N-acetyl- $\alpha$ -neuraminosyl-(2 $\rightarrow$ 6)]-O-2-(acetylamino)-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 3)- (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C50 H82 N4 O37  
 SR CA  
 LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

/ Structure 1 in file .gra /

/ Structure 2 in file .gra /

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1907 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
2.34	5.48

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006  
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FILE COVERS 1907 - 13 Jun 2006 VOL 144 ISS 25  
FILE LAST UPDATED: 12 Jun 2006 (20060612/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/infopolicy.html>

=> d his

(FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006)

FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006  
E "RM2"/CN 25  
E "RM-2"/CN 25

L1 FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006  
1 S US 20050221397/PN  
SEL RN

L2 FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006  
1 S E1

FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006

=> s 12  
L3 2 L2

=> d ibib 1-2

L3 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1078089 CAPLUS  
 DOCUMENT NUMBER: 143:344596  
 TITLE: Rm2 antigen (beta1,4-galnac-disialyl-lc4) as prostate cancer-associated antigen  
 INVENTOR(S): Saito, Seiichi  
 PATENT ASSIGNEE(S): Northern Advancement Center for Science & Technology, S. Korea  
 SOURCE: U.S. Pat. Appl. Publ., 13 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005221397	A1	20051006	US 2004-812357	20040330
WO 2005098434	A2	20051020	WO 2005-US10221	20050325

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
 RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-812357 A 20040330

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:373084 CAPLUS  
 DOCUMENT NUMBER: 142:408646  
 TITLE: RM2 antigen (β1,4-GalNAC-disialyl-Lc4) as a new marker for prostate cancer  
 AUTHOR(S): Saito, Seiichi; Egawa, Shin; Endoh, Mareyuki; Ueno, Seiji; Ito, Akihiro; Numahata, Kenji; Satoh, Makoto; Kuwao, Sadahito; Baba, Shiro; Hakomori, Senitiroh; Arai, Yoichi  
 CORPORATE SOURCE: Department of Urology, Tohoku University Graduate School of Medicine, Sendai, Japan  
 SOURCE: International Journal of Cancer (2005), 115(1), 105-113  
 CODEN: IJCNW; ISSN: 0020-7136  
 PUBLISHER: Wiley-Liss, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file pctfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	3.20	8.68

FILE 'PCTFULL' ENTERED AT 14:39:42 ON 13 JUN 2006  
 COPYRIGHT (C) 2006 Univentio

FILE LAST UPDATED: 13 JUN 2006 <20060613/UP>  
 MOST RECENT UPDATE WEEK: 200623 <200623/EW>  
 FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOW AVAILABLE IN THIS FILE.  
SEE  
<http://www.stn-international.de/stndatabases/details/ipc-reform.html> >>>

>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE  
(last updated April 10, 2006) <<<

=> s RM2  
L4 397 RM2

=> s antibod?  
L5 88553 ANTIBOD?

=> s 15 and 14  
L6 95 L5 AND L4

=> s cancer? or tumor? or neoplas?  
78950 CANCER?  
65926 TUMOR?  
22900 NEOPLAS?  
L7 98312 CANCER? OR TUMOR? OR NEOPLAS?

=> s 16 and 17  
L8 67 L6 AND L7

=> s prostate and 18  
24530 PROSTATE  
421 PROSTATES  
24544 PROSTATE  
(PROSTATE OR PROSTATES)  
L9 23 PROSTATE AND L8

=> s 19 not py>2002  
408573 PY>2002  
L10 8 L9 NOT PY>2002

=> d ibib 1-8

L10 ANSWER 1 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 2002056022 PCTFULL ED 20020725 EW 200229  
TITLE (ENGLISH): DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR  
TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND  
METHODS FOR TREATMENT OF CANCER  
TITLE (FRENCH): MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE  
MEDICAMENTS POUR L'INHIBITION DE LA  
TUMORIGENESE, ET COMPOSITIONS ET PROCEDES POUR  
LE TRAITEMENT DU CANCER  
INVENTOR(S): BAMDAD, Cynthia, C., 142 Church Street, Newton, MA  
02458, US;  
BAMDAD, R., Shoshana, 142 Church Street, Newton, MA  
02458, US  
PATENT ASSIGNEE(S): MINERVA BIOTECHNOLOGIES CORPORATION, 142 Church Street,  
Newton, MA 02458, US [US, US]  
AGENT: POMIANEK, Michael, J.\$, Wolf, Greenfield & Sacks, P.C.,  
600 Atlantic Avenue, Boston, MA 02210\$, US  
LANGUAGE OF FILING: English  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
-----		
WO 2002056022	A2	20020718

DESIGNATED STATES  
W:

AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR



RW (ARIPO):  
RW (EAPO):  
RW (EPO):

CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID  
IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD  
MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI  
SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW  
GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW  
AM AZ BY KG KZ MD RU TJ TM  
AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE  
TR

RW (OAPI):  
APPLICATION INFO.:  
PRIORITY INFO.:

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG  
WO 2001-US44782 A 20011127  
US 2000-60/253,361 20001127  
US 2000-60/255,370 20001213  
US 2000-60/256,027 20001215  
US 2000-60/258,157 20001222  
US 2001-60/259,615 20010103  
US 2001-60/260,186 20010105  
US 2001-60/266,169 20010202  
US 2001-60/266,929 20010206  
US 2001-60/278,093 20010323  
US 2001-60/289,444 20010507  
US 2001-60/294,887 20010531  
US 2001-60/298,272 20010614

L10 ANSWER 2 OF 8  
ACCESSION NUMBER:  
TITLE (ENGLISH):  
TITLE (FRENCH):  
INVENTOR(S):

PCTFULL COPYRIGHT 2006 Univentio on STN  
2001042786 PCTFULL ED 20020827  
SYSTEM FOR CELL BASED SCREENING : CELL SPREADING  
SYSTEME DE CRIBLAGE A BASE DE CELLULES

PATENT ASSIGNEE(S):

SAMMAK, Paul;  
DUENSING, Thomas, D.;  
RUBIN, Richard  
CELLOMICS, INC.;  
SAMMAK, Paul;  
DUENSING, Thomas, D.;  
RUBIN, Richard  
Patent

DOCUMENT TYPE:  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001042786	A2	20010614

DESIGNATED STATES  
W:

AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE  
DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE  
KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX  
NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA  
UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG  
ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI  
FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA  
GN GW ML MR NE SN TD TG

APPLICATION INFO.:  
PRIORITY INFO.:

WO 2000-US33308 A 20001208  
US 1999-60/170,087 19991209

L10 ANSWER 3 OF 8  
ACCESSION NUMBER:  
TITLE (ENGLISH):  
TITLE (FRENCH):  
INVENTOR(S):

PCTFULL COPYRIGHT 2006 Univentio on STN  
2001000247 PCTFULL ED 20020828  
PEPTIDE-LIPID CONJUGATES, LIPOSOMES AND LIPOSOMAL DRUG  
DELIVERY  
CONJUGUES PEPTIDES-LIPIDES, LIPOSOMES ET APPORT DE  
MEDICAMENTS LIPOSOMIQUES  
MEERS, Paul;  
PAK, Charles;  
ALI, Shaukat;  
JANOFF, Andrew;  
FRANKLIN, J., Craig;  
ERUKULLA, Ravi;  
CABRAL-LILLY, Donna;  
AHL, Patrick

PATENT ASSIGNEE(S): THE LIPOSOME COMPANY, INC.  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001000247	A1	20010104

DESIGNATED STATES  
W:

AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ  
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS  
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN  
MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR  
TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ  
TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK  
ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM  
GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US16248 A 20000613  
PRIORITY INFO.: US 1999-09/343,650 19990629

L10 ANSWER 4 OF 8

ACCESSION NUMBER:

TITLE (ENGLISH):

TITLE (FRENCH):

INVENTOR(S):

PATENT ASSIGNEE(S):

LANGUAGE OF PUBL.:

DOCUMENT TYPE:

PATENT INFORMATION:

PCTFULL COPYRIGHT 2006 Univentio on STN  
2000072686 PCTFULL ED 20020515  
REGULATION OF SYSTEMIC IMMUNE RESPONSES UTILIZING  
CYTOKINES AND ANTIGENS  
REGULATION DE LA REPOSE IMMUNITAIRE SYSTEMIQUE A  
L'AIDE DE CYTOKINES ET D'ANTIGENES  
HARDY, Steve;  
DRANOFF, GlennRP : NAKAMURA, Dean  
CELL GENESYS, INC.  
English  
Patent

NUMBER	KIND	DATE
WO 2000072686	A1	20001207

DESIGNATED STATES  
W:

AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ  
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS  
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN  
MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR  
TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ  
TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK  
ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM  
GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US15190 A 20000602  
PRIORITY INFO.: US 1999-09/324,707 19990602

L10 ANSWER 5 OF 8

ACCESSION NUMBER:

TITLE (ENGLISH):

TITLE (FRENCH):

INVENTOR(S):

PATENT ASSIGNEE(S):

LANGUAGE OF PUBL.:

DOCUMENT TYPE:

PATENT INFORMATION:

PCTFULL COPYRIGHT 2006 Univentio on STN  
2000057899 PCTFULL ED 20020515  
THROMBOSPONDIN-2 AND USES THEREOF  
LA THROMBOSPONDINE-2 ET SES UTILISATIONS  
DETMAR, Michael;  
STREIT, Michael  
THE GENERAL HOSPITAL CORPORATION;  
DETMAR, Michael;  
STREIT, Michael  
English  
Patent

NUMBER	KIND	DATE
WO 2000057899	A1	20001005

DESIGNATED STATES  
W:

AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ  
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS  
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN  
MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT

TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ  
 UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES  
 FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA  
 GN GW ML MR NE SN TD TG  
 APPLICATION INFO.: WO 2000-US7835 A 20000324  
 PRIORITY INFO.: US 1999-60/127,221 19990331

L10 ANSWER 6 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN  
 ACCESSION NUMBER: 2000029433 PCTFULL ED 20020515  
 TITLE (ENGLISH): 12-25-KDA BACTERIAL PROTEINS AND THEIR 116-58 KDA  
 POLYMERS FOR USE E.G. IN ANTI-TUMOR VACCINES  
 TITLE (FRENCH): PRODUIT  
 INVENTOR(S): KISLITCHKINE, Nikolay  
 PATENT ASSIGNEE(S): TOLIN AS;  
 JONES, Elizabeth, Louise;  
 KISLITCHKINE, Nikolay  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000029433	A2	20000525

DESIGNATED STATES  
 W:

AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE  
 DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE  
 KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX  
 NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA  
 UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW  
 AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR  
 GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW  
 ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-GB3852 A 19991118  
 PRIORITY INFO.: RU 1998-98120511 19981118  
 GB 1999-9908663.9 19990415

L10 ANSWER 7 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN  
 ACCESSION NUMBER: 1997033908 PCTFULL ED 20020514  
 TITLE (ENGLISH): LYTIC PEPTIDES  
 TITLE (FRENCH): PEPTIDES LYTIQUES  
 INVENTOR(S): RIVETT, Donald, Edward;  
 HUDSON, Peter, John;  
 WERKMEISTER, Jerome, Anthony  
 PATENT ASSIGNEE(S): COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH  
 ORGANISATION;  
 RIVETT, Donald, Edward;  
 HUDSON, Peter, John;  
 WERKMEISTER, Jerome, Anthony  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9733908	A1	19970918

DESIGNATED STATES  
 W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
 ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS  
 LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG  
 SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ  
 UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR  
 GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML  
 MR NE SN TD TG

APPLICATION INFO.: WO 1997-AU160 A 19970313  
 PRIORITY INFO.: AU 1996-PN 8614 19960313

L10 ANSWER 8 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1995019169 PCTFULL ED 20020514  
 TITLE (ENGLISH): TREATMENT OF PLATELET DERIVED GROWTH FACTOR RELATED  
 DISORDERS SUCH AS CANCERS USING INHIBITORS OF  
 PLATELET DERIVED GROWTH RECEPTOR  
 TITLE (FRENCH): TRAITEMENT DE TROUBLES LIES AU FACTEUR MITOGENIQUE  
 PLAQUETTAIRE TELS QUE LES CANCER, UTILISANT  
 DES INHIBITEURS DU RECEPTEUR DE FACTEUR MITOGENIQUE  
 PLAQUETTAIRE  
 INVENTOR(S): HIRTH, Klaus, Peter;  
 SCHWARTZ, Donna, Pruess;  
 MANN, Elaina;  
 SHAWVER, Laura, Kay;  
 KERI, Gyorgy;  
 SZEKELY, Istvan;  
 BAJOR, Tamas;  
 HAIMICHAEL, Janis;  
 ORFI, Laszlo;  
 LEVITZKI, Alex;  
 GAZIT, Aviv;  
 ULLRICH, Axel;  
 LAMMERS, Reiner;  
 KABBINAVAR, Fairouz, F.;  
 SLAMON, Dennis, J.;  
 TANG, Cho, Peng  
 PATENT ASSIGNEE(S): SUGEN, INC.;  
 BIOSIGNAL LTD.;  
 YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW  
 UNIVERSITY OF JERUSALEM;  
 MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER  
 WISSENSCHAFTEN E.V.;  
 REGENTS OF THE UNIVERSITY OF CALIFORNIA  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
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DESIGNATED STATES

W:

AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE  
 HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL  
 NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN KE MW SD  
 SZ AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF  
 BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1995-US363 A 19950106  
 PRIORITY INFO.: US 1994-8/179,570 19940107

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L10 ANSWER 1 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN  
 TIEN DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR  
 TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR  
 TREATMENT OF CANCER  
 TIFR MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE MEDICAMENTS POUR  
 L'INHIBITION DE LA TUMORIGENESE, ET COMPOSITIONS ET PROCEDES  
 POUR LE TRAITEMENT DU CANCER  
 ABEN . . . a series of compositions, methods, kits, articles and species  
 associated primarily with the diagnosis and/or treatment of cell  
 proliferation, specifically cancer. Cell proliferation  
 associated with aberrant expression of MUCI is particularly focused  
 upon. Mechanisms associated with MUCI cell proliferation are discussed.  
 ABFR . . . de procedes, de troussees, d'articles et d'especes associes  
 principalement au diagnostic et/ou au traitement de la proliferation  
 cellulaire, notamment du cancer. L'invention concerne en  
 particulier la proliferation cellulaire associee a l'expression

aberrante de MUC1, ainsi que des mecanismes associes a la. . .

DETD DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR  
TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR  
TREATMENT OF CANCER  
Related Applications  
This non-provisional application claims the benefit under Title 35,  
U.S.C.

#### Field of the Invention

The invention relates to assays using shed cell surface receptor  
interchain binding  
regions and cleavage products for cancer diagnosis, and for  
the evaluation of cancer  
treatment and using the portion of the receptor that remains on the cell  
as a molecular  
target for cancer therapeutics.

#### Background of the Invention

Many of the biomolecular interactions that promote tumorigenesis  
involve cell  
surface proteins that mediate both intra- and intercellular signaling.  
Tumor markers are  
proteins on the surface of a cell that are exclusively expressed,  
over-expressed or show  
an altered expression pattern as a result of transformation to a  
neoplastic state. The  
surface concentration of certain tumor markers has been  
correlated to the progression of  
cancer. For example, the interaction between the cell surface  
receptor  $\alpha$ VP3 and the cell  
adhesion molecule vitronectin has been implicated in angiogenesis. . .

Integrins and cancer. Curr Opin Cell Biol, 1996, 8(5):

724-730; Vailhe B, Ronot X,

Tracqui P, Usson Y, Tracqui L: In vitro angiogenesis is. . .

Cell surface receptors, that have been linked to cancer, make  
up an important  
class of therapeutic targets. Many pharmaceutical companies are actively  
involved in  
screening drug libraries for compounds that bind to and block these cell  
surface  
receptors. For example, an important drug used to treat breast  
cancer is Herceptin  
(Pegram M, Lipton A, Hayes D, Webber B, Baselga J, Tripathy D, Baly D,  
Baughman S,  
Twaddell T, Glaspy J, Slamon D: Phase II study of receptor-enhanced  
chemosensitivity  
using recombinant humanized anti-p 185 Her2/neu monoclonal  
antibody plus cisplatin, in  
patients with Her2/neu-overexpressing metastatic breast cancer  
refractory to  
chemotherapy treatment, J Clin Oncol, 1998, 16(8): 2659-2671). This  
drug binds to and  
blocks HER2/neu (Ross J, Fletcher J: review, The Her2/neu oncogene in  
breast cancer.

for therapy. Stem Cells, 1998, 16(6): 413-

428) which is a cell surface receptor that is over-expressed on 30% of  
breast tumors.

myeloma cells and is induced

by dexamethasone. Blood, 1999, 93(4): 1287-1298), is especially  
interesting since it is

aberrantly expressed on many human tumors, including 80% of breast tumors, and on a significant percentage of prostate, lung, ovarian, colorectal and perhaps brain, cancers.

epithelium, MUC I is clustered at the apical border and is not expressed over other portions of the cell. However, in tumor cells, the receptor is homogeneously over-expressed over the entire cell surface (Kufe D., Inghirami G., Abe M., Hayes D, Justi-Wheeler H, Schlom J: Differential reactivity of a novel monoclonal antibody (DF3) with human malignant versus benign breast tumors. Hybridoma, 1984, 3.

223-232), rather than just at the apical border. It is also known that women with breast cancer have elevated levels of shed MUC 1 receptor in their blood stream. Extracellular portions of the MUC I receptor are cleaved. . . . least one enzyme, and released into the blood stream. Levels of shed MUC I receptor in serum are measured to track breast cancer patients for recurrence. However, the method is too variable and insensitive to be used as a general diagnostic.

Until now, the mechanistic link between the MUC I receptor and tumorigenesis has not been understood. Attempts to correlate the number of repeat units, which varies from person to person, and susceptibility to cancer failed. Investigations of a possible connection, between glycosylation of the MUC1 receptor and cancer, produced conflicting results. Importantly, until now, a functional ligand(s) for the extracellular portion of the MUC 1 receptor has not been identified.

Absent an understanding of the mechanism of the MUC I receptor, and how it triggers tumorigenesis, it has not been possible to design or identify therapeutics that interfere with the disease-associated function of this receptor. Indeed, currently there. . .

The present invention describes discoveries that elucidate critical aspects of the mechanism by which WC I triggers cell proliferation and tumorigenesis. These discoveries provide novel molecular targets for drug screening assays which the inventors have used to identify compounds that inhibit the WC. . .

of the Invention

The present invention provides a variety of kits, methods, compositions, peptide species and articles associated with cell proliferation, specifically cancer. The invention involves primarily techniques and components for the diagnosis and treatment of cancer.

Another method of the invention involves treating a subject having cancer or being at risk for developing cancer, the method comprises administering to the subject an

agent that reduces cleavage of a cell surface receptor.

Another method of the invention for treating a subject having cancer or at risk for developing cancer comprises administering to the subject an agent that reduces cleavage of a cell surface receptor interchain binding region from the cell.

comprises determining an amount of cleavage of a cell surface receptor interchain binding region from a cell surface, and evaluating indication of cancer or potential for cancer based upon the determining step.

determining a site of cleavage of a cell surface receptor in a sample from a subject, and evaluating an indication of cancer or potential for cancer based upon the determining step.

Another method of the invention involves treating a subject to reduce the risk of or progression of cancer. The method comprises administering to a subject, who is known to be at risk for cancer or is diagnosed with cancer, an agent for inhibiting interaction of an activating ligand with a portion of a cell surface receptor that interacts with the activating.

Another method of the invention involves treating a subject to reduce the risk of or progression of cancer. The method comprises administering to a subject, who is known to be at risk of cancer or is diagnosed with cancer, an agent for preventing clustering of portions of cell surface receptors that interact with an activating ligand such as a growth factor.

Another method involves diagnosing a physiological state indicative of cancer or potential for cancer. The method comprises determining a specific cleavage site of MUC I distinguishable from a different cleavage state of MUC I.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC 1 . comprising administering to the subject etomoxir in an amount effective to reduce tumor growth.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising administering to the subject L-cc-methyl-dopa in an amount effective to reduce tumor growth.

Another method of the invention for treating a subject having cancer characterized by the aberrant expression of MUC I, comprises administering to the subject calcimycin in an amount effective to reduce tumor

growth.

Another method for treating a subject having a cancer characterized by the aberrant expression of MUC 1, comprises administering to the subject butylindazole in an amount effective to reduce tumor growth.

imply a disease-related cleavage site on the MUCI receptor;

Fig. 4 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes the receptor, enhances cell proliferation in a manner typical of a growth factor/receptor -

antibody interaction;

Fig. 5 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes the receptor, dramatically enhances. . . used to detect inhibitors of the MUC 1 -Ligand

interaction;

Fig. 13 shows a histogram illustrating the selective inhibition of proliferation of tumor

cells that aberrantly express the WC I receptor, in response to treatment with

compounds of the invention, and lack of an effect. . . of the WC I receptor and a multimerizing ligand(s);

Fig. 15 shows a histogram illustrating the selective inhibition of proliferation of tumor

cells that aberrantly express the WC I receptor, in response to treatment with drugs that

specifically inhibit MUC1 positive cells;

Fig. 16 shows. . . to treatment with drugs that non-specifically inhibit cell proliferation;

Fig. 17 shows a histogram illustrating that drugs that selectively inhibit proliferation of

tumor cells that aberrantly express the WC I receptor bind to the PSMGFR, while drugs

that non-selectively inhibit cell proliferation do not;

Fig. 18 is a graph showing that the inhibition of WC 1 -dependent cell proliferation

induced by an anti-tumor drug identified in accordance with the invention, is modulated

when a synthetic peptide, corresponding to the portion of MUC I that. .

a mechanism in which this portion is made

accessible to the ligand upon MUC I cleavage at a site associated with tumorigenesis that

causes release of the IBR from the cell.

shed, or cleaved. The cleaved IBR of interest is a

disease-associated cleavage, i.e. that type of cleavage that can result in cancer.

ratio with the IBR and forms part of the portion of MUC I that is shed upon cleavage in healthy and tumorigenic cells.

type of interaction that occurs

between pairs of molecules including proteins, nucleic acids, glycoproteins,

carbohydrates, hormones and the like. Specific examples include



antibody/antigen,  
antibody/hapten, enzyme/substrate, enzyme/inhibitor,  
enzyme/cofactor, binding  
protein/substrate, carrier protein/substrate, lectin/carbohydrate,  
receptor/hormone,  
receptor/effector, complementary strands of nucleic acid,  
protein/nucleic acid  
repressor/inducer, ligand/cell surface receptor, virus/ligand, etc.

the host system includes a synthetic species such as a polymer,  
dendrimer,  
etc., or a naturally-occurring species, for example an IgM  
antibody, which is not simply  
naturally present in the host system but is added to the host system  
from a source  
external to. . .

a dimer, a  
tetramer, a higher multimer, or a complex comprising a plurality of  
molecular species. In  
the context of MUC I tumor cells, an activating ligand can be  
a species produced by the  
cells that interacts with the MGFRs on the surface of the WC 1  
tumor cells in a manner  
that effects inductive multimerization.

A MUC I presenting cell refers to both non-cancerous and  
cancerous cells  
expressing MUC I and/or MGFRs on the surface. A WC I tumor  
cell or NWC 1

cancer cell or cancerous MUC1 cell refers to a  
cancerous tumor cell that aberrantly  
expresses MUC I and/or MGFR on its surface.

limited to, a  
binding species such as a peptide synthesized on a polystyrene bead, a  
binding species  
specifically biologically coupled to an antibody which is  
bound to a protein such as  
protein A, which is attached to a bead, a binding species that forms. . .

cover in this context, means that there is no portion of the surface or  
30 region that directly contacts a protein, antibody, or other  
species that prevents complete,  
direct coverage with the SAM. I.e. in preferred embodiments the surface  
or region  
includes, across its. . .

The term cancer, as used herein, may include but is not  
limited to: biliary tract

cancer; bladder cancer; brain cancer  
including glioblastomas and medulloblastomas;  
breast cancer; cervical cancer; choriocarcinoma;  
colon cancer; endometrial cancer;  
esophageal cancer; gastric cancer; hematological  
neoplasms including acute lymphocytic  
and myelogenous leukemia; multiple myeloma; AIDS-associated leukemias  
and adult T-  
cell leukemia lymphoma; intraepithelial neoplasms including  
Bowen's disease and  
Paget's disease; liver cancer; lung cancer;  
lymphomas including Hodgkin's disease and  
lymphocytic lymphomas; neuroblastomas; oral cancer including  
squamous cell

carcinoma; ovarian cancer including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squamous cell cancer; testicular cancer including germinal tumors such as seminoma, non-seminoma (teratomas, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor. Preferred cancers are; breast, prostate, lung, ovarian, colorectal, and brain cancer.

The term cancer treatment as described herein, may include but is not limited to: chemotherapy, radiotherapy, adjuvant therapy, or any combination of the aforementioned methods.

Another treatment for cancer is surgery, which can be utilized either alone or in combination with any of the aforementioned treatment methods. One of ordinary.

An agent for prevention of cancer or tumorigenesis means any agent that counteracts any process associated with cancer or tumorigenesis described herein. For example, an agent that interacts with (e.g., binds to) to MGFR thereby reducing or preventing interaction, with.

in a cell-free assay containing the enzyme and WC I receptors, and the rate or position of cleavage measured by antibody probing, Polymerase Chain Reaction (PCR), or the like. Alternatively, without first identifying enzymes that affect WC I, agents are screened against cells. present WC I, the supernatant removed, and the cell remain tested for accessibility of the MGFR portion, e.g. using a labeled antibody to the MGFR. Agents can be identified from commercially available sources such as molecular libraries, or rationally designed based on known agents.

reduces cleavage of the WC I receptor at any location. Such an agent can be used to treat a subject having cancer or at risk for developing cancer because if cleavage is prevented, then the accessibility of the MGFR, a functional receptor associated with cancer, is reduced or prevented. Such agents can be selected by exposing cells to a candidate agent and determine, in the supernatant,

A subject, as used herein, refers to any mammal (preferably, a human), and preferably a mammal that may be susceptible to tumorigenesis or cancer associated with the aberrant expression of MUC I. Examples include a human, non-human

primate,  
cow, horse, pig, sheep, goat, dog, or cat.. . .

The present invention involves, generally, novel molecular targets for drug screening, therapeutics and diagnostics related to cancers that are characterized by the aberrant expression of a class of cell surface receptors characterized by interchain binding regions. One such set of cancers are those characterized by the aberrant expression of MUC I. Much of the description of the invention herein involves. . . to identify other cell surface receptors that function by this or a similar mechanism, and to apply the invention to those cancers characterized by aberrant expression of receptors. The invention is based on a novel mechanism involving cell surface receptors that have regions that. . .

and progressing away from the cell. In at least one U.S. provisional patent application (earlier application(s)) filed by the same inventors, entitled Tumor Markers and Drug Screening for Tumorigenesis Inhibition, relating to MUC I diagnostics and other techniques, at least one region of MUC I was defined differently. It is to. . .

Cleavage of MUC1 may occur at a site at or near the C-terminal boundary of the IBR in tumor or cancer cells (between the cell and the IBR), releasing the IBR from the cell. Alternatively, cleavage of WC1 may occur within the IBR itself to cause sufficient disrupting of the IBRs such that the. . .

from interacting with the MGFR portion of the receptor, which is proximal to the cell relative to the IBR. In a cancerous or tumor cell, this reticulum may be lost, allowing ligand interaction with the MGFR.

proliferation; and (b) blocking the interaction of this portion of the WC I receptor (MGFR) with its ligand(s), blocks cell proliferation. When tumor cell lines, in which the WC I receptor is homogeneously expressed across the entire cell surface, are treated with an IgG antibody raised against the MGFR portion of the WC I receptor, the rate of cell proliferation is greatly enhanced, see Fig. 5. Since IgG antibodies are bivalent, i.e. one antibody simultaneously binds to two adjacent MGFR portions on the cell surface, these results demonstrate that the antibody acts as an activating ligand, mimicing the effect of a growth factor, which dimerizes MGFR portions, and thus triggers a cell. . . of the receptor with a monomeric composition, thus preventing inductive multimerization and subsequent signaling cascades. For example, a single chain, or monovalent, antibody raised against the MGFR portion of the MUC1 receptor would function as an effective anti-cancer therapeutic. Another therapeutic strategy is to block the activity of enzymes that modify

the receptor, which may be required for some ligand. . . .

histidine tag of the peptide, the beads were then incubated with lysates and supernatants from a variety of cell types, including cancer cell lines that overexpress MUC1. Enzyme inhibitors such as PMSF were added to some of the lysates and supernatants to circumvent problems. . . .

containing some or all of these ligand species. In one aspect, the invention involves modification and use of the above species as anti-cancer agents.

a protein known as Metastasis Inhibition Factor NM23, which has been implicated in both the promotion and inhibition of metastasis of human

cancers. Whether the role of NM23 is a tumor suppressor or promoter may depend on the type of cancer. In ovarian, colon and neuroblastoma tumors, NM23 overexpression has been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz R, Centeno

MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline ovarian

carcinoma, *Anticancer Res*, 1996; 16(3A): II 97-202). However, breast cancer studies

indicate that reduced expression of NM23 correlates with poor prognosis (Mao H, Liu H,

Fu X, Fang Z, Abrams J, Worsham MJ, Loss of NM23 expression predicts distal

metastases and poorer survival for breast cancer, *Int J Oncol* 2001 Mar; 18(3):587-91).

NOT

added to lysate) corresponded to more than one protein species, including 14-3-3, which

is a signaling protein implicated in many cancers, and cathepsin D, which is a protease

and is also implicated in tumor progression. 14-3-3 exists as a dimer and can

simultaneously bind to two, identical phospho-serine peptides. This protein has been shown to. . . .

a high degree

of homology to beta-lipotropin (Odell W, Wolfsen A, Bachelot 1, and Hirose F, (1979)

Ectopic production of lipotropin by cancer *The American Journal of Medicine* 66; pgs.

the position of

enzyme cleavage is associated with receptor clustering, accessibility of adjacent portions

of the receptor to putative ligands, and thus cancer. Agents that modulate the activity of

this enzyme may be potent anti-cancer agents. Additionally, an early diagnostic test for

cancers that aberrantly express MUC 1 may be based on detecting the portion of MUC 1

that self-aggregates (113R) circulating in bodily. . . . cell

surface after the release of the portion that self-aggregates (IBR - some or all of the

PSIBR sequence) may be potent anti-cancer drugs. In addition, agents that block binding

of the natural ligand to the remaining portion after the release of the IBR, . . . biomolecules and to artificially cluster the MGFRs. Another alternative agent, which can be used to artificially cluster the MGFRs is an IgM antibody raised against the MGFR or PSMGFR. This artificially-induced clustering may serve to keep the cytoplasmic tails clustered to prevent interaction with intracellular. . .

One aspect of the invention involves a novel drug screening assay, that identifies therapeutics that interfere with the proliferation of tumor cells that aberrantly express MUC L. The drug screen makes use of the new molecular target for cancer that is disclosed herein. Another aspect of the invention involves therapeutics identified by the drug screen. Yet another aspect of the invention involves methods for diagnosing MUC I+ cancers, which is based upon the mechanism elucidated by the inventors.

assay which can rapidly identify agents that interrupt the interaction between the MGFR and its ligand(s) and thus can be used as cancer therapeutics, (see Example 5a and Fig. 12 for details).

60/317,302 and 60/317,314, both filed on September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER.

Agents so identified may be potent anti-cancer agents either in monomeric form or as polymers or dendrimers. Drug libraries and peptide libraries can be screened for molecules that inhibit. . .

its ligands. These methods include but are not limited to phage display methods, yeast two-hybrid system, sandwich assays, surface plasmon resonance-based assays, antibody-based assays, peptide bead assays for testing with drug libraries, bead assays, GFP-reporter assays, and the like. Ligands to the MGFR portion.

used to block binding of the remaining extracellular portion of cleaved MUC I to its natural ligand, and can potentially inhibit cancer growth.

of the invention is a drug screening assay for identification of drugs that can be useful for prevention and/or treatment of cancer by altering the cleavage state of WC 1 receptors on cells. In such assays, described in more detail below, cultured cells are. . . and/or dosage or other conditions involving exposure to the drugs. These cells can be derived from a particular patient, or can be tumor-associated or non-tumor-associated cell lines. Customized therapeutic protocols can be determined for a particular patient in this manner. The invention involves, in one aspect, treating. . . below, shown to affect the cleavage state of WC I of the patient's cells in a manner that

prevents, inhibits, or reverses cancer.

suspected that the incorrect cleavage of WC 1 on the surface of the cell causes the cascade leading to proliferation and tumorigenesis, it would be advantageous to test candidate drugs in a whole cell assay for their ability to affect enzyme cleavage or the.

Colloids bearing an antibody, natural ligand, or small molecule that binds to either the cleaved portion of WC I, or the remaining extracellular portion (plus.

contained within the shed fragment. The aggregation potential of peptides released into the cell media is tested by adding colloids bearing an

antibody to a sequence distal from the self-aggregating portion, but not a repeat sequence. In this way, antibody-presenting colloids would attach to upstream regions of MUCL If the self-aggregating region was also attached to the released fragment, then this would.

of these portions or other structural constraint that inhibits their association with factors that promote cell proliferation. Alternatively, IgM-type monoclonal or polyclonal antibodies raised against the MGFR or PSMGFR could be utilized. Each anti-MGFR IgM antibody could be able to aggregate ten MGFRs on the cell surface to form preventative clusters.

I receptor can similarly be modified with other therapeutic agents. In this way, such a therapeutic can be directed to the tumor cells. For example, an agent that binds to the MGFR region of the WC 1 receptor can be modified with a radioactive substance to destroy tumor cells that aberrantly express the WC I receptor. Other toxic substances, such as ricin, as well as other therapeutics, can be. that bind to the MGFR could be modified to present a imaging agent for use in diagnostic imaging of MUC 1+ tumors and metastases. Such ligands can also, alternatively, be modified to act as drugs that can be useful for prevention and/or treatment of cancer. In one embodiment, a ligand, which in its unmodified form binds to multiple MGFRs causing inductive multimerization, is modified to remove or.

The discoveries presented herein: (1) that the IBR of MUC I self-aggregates; (2) that an antibody that dimerizes adjacent MGFR portions of the MUC I receptor leads to proliferation of WC I presenting tumor cells; and (3) that proliferation of MUC I presenting tumor cells can be inhibited by treatment with agents that target the MGFR and block the MGFR against interaction with a ligand, the cell that WC I remains clustered, and the MGFR is inaccessible to ligands

such  
as growth factors, and in a tumor cell, MUC I cleavage occurs  
such that enough of the  
IBR is cleaved from the cell such that WC I does. . .

The above-mentioned mechanistic model predicts that in a subject with a  
WC I -  
dependent tumor or who is prone to developing such a  
tumor, the portion of the MUC I  
receptor that is shed will contain the IBR region of the receptor,  
leaving the MGFR  
portion. . .

The cleavage state will differ between a healthy cell and a cell with  
tumor potential. The  
cleavage state determination can involve determining whether cleavage  
occurs in a  
manner such that the normal interaction between the IBRs. . .

and/or a signaling entity. Generally, an assay as  
described in WO 00/43791 or WO 00/34783 can be used. In a specific  
example,

antibodies to a portion of MUC I that would remain fastened to  
the IBR if the IBR is  
cleaved from the cell, such as antibodies to the repeats  
domain, are fastened to colloids.

The discovery that tumor cells can be treated with an agent  
that binds to the  
MGFR of MUC 1, or a ligand of MGFR, in a manner that inhibits cell  
proliferation leads  
to the conclusion that, in a diseased cell (a cancerous cell  
or a cell with potential for  
becoming cancerous), cleavage of MUC I occurs in a manner that  
allows MGFR to  
interact with at least one ligand in a manner that promotes  
tumorigenesis or cancer.

separated from the cell. The amounts of various receptor regions  
may be determined with any type of binding assay, e.g. an  
antibody-binding assay. For  
example, antibodies that specifically bind to the constant  
region or the repeats may be  
attached to surfaces (e.g. magnetic beads) to preconcentrate shed MUC I  
receptors prior  
to determining levels of IBR present. Then, for example, after  
pre-concentration of  
circulating MUC I receptors, antibodies to the IBR and  
antibodies to the constant region  
can be allowed to bind to the cleaved receptors, and determination of  
the ratio of binding  
of these antibodies reveals the ratio of IBR present relative  
to constant region present in  
the cleaved receptors, which in turn reveals the amount. . . IBR  
relative to constant region present) for  
detecting IBR at a cell surface is an indicator of the presence of a  
tumor or the potential  
for the development of a tumor. A ratio that approaches 1: 1  
when detecting these  
regions in shed receptors is likewise an indicator of cancer  
potential. This determination  
can indicate potential for tumor formation, existence of a  
tumor, progression of  
tumorigenesis, etc., and can thereby serve as a diagnostic  
and/or a evaluator of treatment

for tumorigenesis

Another diagnostic aspect of the invention involves. . . assay or a colloid bead assay (See above discussion and Examples, below). Alternative techniques involve determining the presence of the IBR using antibody probing assays, hybridization, PCR Reverse Transcriptase PCR (rtPCR), Ligase Chain Reaction (LCR), cycling probe technology, etc. In a preferred embodiment of the. . .

The determination, in a blood sample, of the amount of cleaved receptor carrying IBR, either involving antibody binding ratios, colloid binding assays, or the like can be made on a bodily fluid sample, such as a blood sample and optionally compared with other samples (e.g. to monitor the subject's progression of tumorigenesis or progression for treatment of the same) and/or controls.

site can be studied without removal of the tissue from the subject). In either of these studies, a primary indicator of tumorigenesis or potential for tumorigenesis is the amount of MGFR at a cell surface accessible to interaction with external agents such as growth factors, etc. This determination can be made, for example, by determining the amount of an antibody to the MGFR region that binds to the sample, either using standard antibody binding study techniques, or by exposing the sample to colloids to which antibodies specific to the MGFR region have been immobilized and determining binding of the colloids to the samples using techniques described in International patent publication numbers WO 00/34783 and WO 00/43791, referenced above. In another technique (perhaps more suited for an excised sample), antibodies to the MGFR region and to the IBR can be exposed to the sample and a determination made of the ratio of binding of each to the sample. A healthy sample will exhibit little or no antibody binding to the MGFR region. A sample indicating tumorigenesis or potential for tumorigenesis will show a non-zero ratio of MGFR antibody binding to IBR antibody binding.

a cell surface (rather than the amount of IBR in a shed portion) in a sample from a subject to evaluate cancer, or the potential to develop cancer in a subject.

information as to whether the IBR remains on the cell surface, or was shed from the cell surface, giving indication of cancer or tumorigenesis or the potential for either, as discussed above. Determining the site of cleavage can be accomplished by using enzyme-amplification methods. .

pre- and post-treatment levels of cleaved cell surface receptor IBR, or cell surface receptor IBR at the surface of a cell, in



cancer cells or tissues may be used to diagnose cancer in a subject or assess the effectiveness of treatment in a cancer patient. In a preferred embodiment the cell surface receptor is MUC 1.

Comparison of the levels of the above-mentioned regions with levels from subjects known to be free of cancer may allow determination of the presence of cancer in the subject. An example, although not intended to be limiting, is that a determination of the presence of elevated levels of . . . in a sample from a subject, when compared to a level determined in samples from control subjects, may suggest the presence of cancer in the subject with elevated levels. Such methods of comparing levels of cancer-associated markers between a sample from a subject and a control sample for diagnostic purposes would be understood by one of ordinary. . .

Examples of such methods include Western blotting, ELISA, antibody precipitation, PCR, LCR, rtPCR, cycling probe technology, and colloidal assays as described in international patent application serial no. PCT/US00/01997, filed 01/25/00, entitled 5Rapid. . .

aspect of the invention, the cleavage state of MUC I can be used to determine progression or regression of a subject's cancer over time. The cleavage state also can be used to assess treatment parameters including, but not limited to: dosage, method of administration,. . .

1 5 Another aspect of the invention involves extremely early-stage cancer diagnosis.

This aspect involves identification of patients who may be at risk for developing tumor or cancer associated with abnormal cleavage of MUC I. These patients may not have developed tumors, but may exhibit a cleavage state indicative of a condition that can lead to cancer. In some instances, the subjects will already be undergoing treatment for 20 cancer, while in other instances the subjects will be without present cancer treatment. A test for a genetic predisposition to cancers characterized by aberrant MUC 1 expression of the invention is based on detecting genetic alterations in the MUC I cleavage enzyme(s), over. . .

The fact that elevated levels of cleaved MUC1 are found in the blood of cancer patients is the basis for a blood test for breast cancer, which is not described herein.

is the identification of compounds that directly bind to the PSMGFR portion of the receptor. Therefore, a sensitive method for diagnosing early tumors is to administer to the patient, compounds that bind to the PSMGFR region that have also been derivatized with contrast or imaging agents. These

compounds will  
agglomerate onto tumors wherein this portion of the NWC I  
receptor is accessible.

one aspect of the invention is directed to methods for  
treating a subject diagnosed with or at risk of developing a  
cancer or tumor characterized  
by the aberrant expression of MUC1. The treatments of the present  
invention involve the  
use of drugs or agents as described herein. That is, one aspect involves  
a series of  
compositions useful for treatment of cancer or tumor  
characterized by the aberrant  
expression of MUC I, including these compositions packaged in kits  
including  
instructions for use of the composition for. . . a description of use  
of the composition for participation in any biological  
or chemical mechanism disclosed herein that is associated with  
cancer or tumor. The kit  
also can include instructions for use of a combination of two or more  
compositions of  
some embodiments of the invention.. . . via another known route of  
drug delivery. These and  
other embodiments of the invention can also involve promotion of the  
treatment of  
cancer or tumor according to any of the techniques  
and compositions and combinations  
of compositions described herein.

even though the patients exhibit indication for treatment of one of the  
compositions of the invention for a condition different from  
cancer or tumor, including  
conditions that can be unrelated to cell proliferation or conditions  
that can accompany  
cell proliferation, cancer, or tumor. That is, if a  
composition of the invention is known  
for treatment of a different condition, some embodiments of the present  
invention also  
involve use of that composition for treatments that accompany cell  
proliferation, cancer,  
or tumor disease where indicated. These and other embodiments  
of the invention can  
include such treatment where the dosage, delivery technique or vehicle,.  
. . . timing of administration, or other  
factor differs from the use of the composition for treatment of the  
condition different  
from cell proliferation, cancer, or tumor. In  
another set of embodiments, treatment of  
cell proliferation, cancer, or tumor with  
compositions of the invention may occur under  
5 conditions that are similar to or overlap the use of compositions of.  
. . . the invention for  
treatment of a different condition, but the compositions of the  
invention are promoted for  
treatments that accompany cell proliferation, cancer, or  
tumor or includes instructions for  
treatments that accompany cell proliferation, cancer, or  
tumor as mentioned above. As  
used herein, promoted includes all methods of doing business including  
methods of  
education, hospital and other clinical instruction,. . . written,  
oral, and electronic communication of any form, associated with  
compositions of the invention in connection with treatments that  
accompany cell  
proliferation, cancer, or tumor. Instructions can

and often do define a component of promotion, and typically involve written instructions on or associated with packaging of compositions. . . .

Subjects for whom certain treatment methods of the invention (with specific compositions directed toward cell proliferation, cancer, or tumor) are not intended are those who are diagnosed with a condition which may already call for treatment with the specific composition. Accordingly, one aspect of the invention involves treatment of cell proliferation, cancer, or tumor with a specific composition disclosed herein for that purpose, not in combination with another agent where the other agent has been taught previously for use in treatment of cell proliferation, cancer, or tumor itself. Another embodiment involves treatment of cell proliferation, cancer, or tumor with this specific composition alone, not in combination with any other active agent. Another embodiment involves treatment of cell proliferation, cancer, or tumor with this specific composition where the use of the composition in the treatment is specifically instructed (through, e.g.

written instructions that can accompany the composition) for the treatment of cell proliferation, cancer, or tumor. In a preferred embodiment of this aspect, the invention involves treatment of cell proliferation, cancer, or tumor with the specific composition where the use of the composition in the treatment is specifically instructed to affect a mechanism associated with cell proliferation, cancer, or tumor as disclosed herein.

treated with drugs useful according to I 9

certain methods of the invention, including patients who are not suffering from cell proliferation, cancer, or tumor and who may or may not be presently indicating susceptibility to cell proliferation, cancer, or tumor. In other words, the preventative treatment preferably is directed to patient populations that otherwise are free of disease symptoms that call for. . . .

NS 1 619 and etomoxir interrupt the interaction of MGFR with its ligand(s) that otherwise would bind to MGFR and promote tumorigenesis.

In this aspect, the invention involves treatment of subjects associated with tumor or cancer associated with aberrant expression of MUC1 with these agents or a combination.

interfering with the MGFR-ligand interaction. All of the compounds inhibited cell proliferation, but roughly half of the compounds were toxic to both tumor cells that presented the MUC I receptor as well as

cells that did not present this receptor. As discussed herein, the. .

to the MGFR

15 portion will have little or no toxic effects. Fusaric acid, L-U-methyl-dopa and etomoxir selectively inhibited proliferation of tumor cells presenting MUC 1 while leaving control cells unaffected, see Fig. 13.

treatment with fusaric acid, but where the call for treatment with fusaric acid did not specifically call for treatment directed toward tumors or cancers associated with the aberrant expression of MUC 1, particularly in the dosages or other specific protocols described previously in U.S. Patent No. 6,127,393. Specific diseases listed in U.S. Patent No. 6,127,393 include skin cancer, breast cancer, prostate cancer, cervical cancer, colon cancer, liver cancer and lung cancer. In one embodiment, the methods of the present invention involve treatment with fusaric acid in dosages lower than that described in U.S.. . .

to the subject any one of calcimycin, fusaric acid, L-cc-methyl-dopa, butylindazole, NS 1619 and etomoxir in an amount effective to lower the risk/prevent/reduce/inhibit tumors or cancer associated with aberrant expression of MUC 1.

the specific route of administration and like factors within the knowledge and expertise of the health practitioner. For example, in connection with tumor or cancer associated with aberrant expression of MUC 1, an effective amount is that amount which prevents interaction of MGFR with its ligand that otherwise. . .

(for agents that act according to that mechanism) so as to slow or halt the development of or the progression of tumor or

cancer associated with aberrant expression of MUC 1. It is preferred generally that a maximum dose be used, that is, the highest. . .

administer higher and more frequent doses of the agent to a subject for example during or immediately following a event associated with tumor or cancer, provided still that such doses achieve the medically desirable result. On the other hand, it may be desirable to administer lower  
20. . .

As noted, different drugs act according to different mechanisms. Drugs according to one mechanism interfere with MGFR binding to a tumorigenesis-promoting ligand, and do so to a particular degree relative to natural conditions for the subject in the absence of the drug.. . .

routes are available. The particular mode selected will depend, of course, upon the particular combination of drugs selected, the severity of the cancer condition being treated, the condition of the patient, and the dosage required for therapeutic efficacy. The methods of this invention, generally.

Parenteral routes include subcutaneous, intravenous, intramuscular, or infusion. Direct injection may be preferred for local delivery to the site of the cancer. Oral administration may be preferred for prophylactic treatment e.g., in a subject at risk of developing a cancer, because of the convenience to the patient as well as the dosing schedule.

(e.g. tissue), such as (e.g. the vascular cell wall), by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein.

Use of a long-term sustained release implant may be particularly suitable for treatment of established cancer conditions as well as subjects at risk of developing a cancer. Long-term release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably 30-60 days. The implant may be positioned at the site of the tumor.

The therapeutic agent may be administered alone or in combination with an anti-cancer drug. If the therapeutic agent is administered in combination the compounds may be administered by the same method, e.g. intravenous, oral, etc. or may be administered separately by different modes, e.g. therapeutic agent administered orally, anti-cancer drug administered intravenously, etc. In one embodiment of the invention the therapeutic agent and the anti-cancer drug are co-administered intravenously. In another embodiment the therapeutic agent and the anti-cancer drug are administered separately.

Anti-cancer drugs that can be co-administered with the compounds of the invention include, but are not limited to Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; . . .

HHHHHHGFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 4)  
Histidine-Tagged Repeat Motif 2 (His-RM2).

GFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 8)  
Repeat Motif 2 (RM2).

Histidine-tagged peptides were synthesized with the sequences shown in table 1 (the various regions of MUC 1). The lyophilized peptides were. . . 2.

Row A contains the His-PSIBR (primary sequence interchain binding region) peptide; Row B contains the His-TR peptide; Row C contains the His-RM2 peptide; Row D contains the His-PSMGFR peptide. Column 1 contains the His-PSIBR peptide; Column 2 contains the His-TR peptide; Column 3 contains the His-RM2 peptide; and Column 4 contains the His-PSMGFR peptide. The solutions were observed for a color change. A change in solution color from . . . sequence of the interchain binding region (PSIBR), self-aggregates in a high affinity interaction, suggesting a mechanism by which the MUC1 receptor confers tumorigenesis.

Example 1b: Relationship Between MUCI Cleavage Site in Tumor Conditions and NWC I Interchain Binding  
This example investigates the ability of peptide sequences near the boundary between the MGFR and PSIBR. . . the MUC 1 receptor to participate in self-aggregation, and thereby elucidates a probable cleavage site of NWC I that is associated with tumorigenesis or cancer.

This strongly suggests that cleavage of the MUC I receptor in tumors or cancers associated with aberrant expression of MUC I occurs at or near the boundary between the PSMGFR and PSIBR sequences, since it is demonstrated herein that in tumor cells that overexpress MUC I, the MGFR is accessible by agents that reduce cell proliferation by inhibiting the interaction between MGFR and . . . otherwise would promote cell proliferation. This also strongly suggests that the IBR is shed in cleavage of MUC I receptor in tumor or cancer associated with aberrant expression of WC I, but is not shed in cleavage of MUC I when WC I is normally expressed. . . That is, that the cleavage site of MUC I is at or near the C-terminal boundary of the IBR in tumor or cancer cells and IBR at or near the N-terminal boundary of the IBR in healthy cells.

In the remaining examples, the mechanism described above for cancer associated with aberrant expression of MUC I, in which an activating ligand (which is a growth factor) binds to multiple MGFRs at . . . which causes proliferation (inductive multimerization), is confirmed. Briefly, the mechanism is confirmed by showing that exposure of cells to a bivalent antibody raised 2o against MGFR induces cell proliferation characterized by a growth/response curve typical of a growth factor/receptor - antibody response (Example 2, below); the activating ligand produced by MUC I -presenting cells binds multiple PSMGFRs, and the amount of activating ligand. . . each cell type is proportional to the amount of MUC I receptor produced by that cell type (Example 3a-b, below); MUC1

tumor cells  
produce a species that is a multimer (Example 4b, below); and drugs  
found to be specific  
for MUC I tumor cells (drugs that inhibit proliferation in MUC  
I tumor cells but not other  
cells) are shown to bind to MGFR at cells, while those that are not  
specific (those that  
inhibit MUC I tumor cells and other cells) are toxic in that  
they bind to the multimeric  
ligand and thereby remove it from interaction with. . .

of the MGFR portion of the WC I receptor triggers enhanced  
Cell Proliferation Consistent with the Mechanism Presented for MUC I  
Tumor Cells  
This example demonstrates the effect of dimerization on the MUC I  
receptor. In  
this example it is shown that exposure of cells to a bivalent  
antibody grown against the  
MGFR region of the MUC I receptor, at varying concentration, results in  
enhanced cell  
proliferation (or lack thereof) consistent with the mechanism presented  
for MUC1 tumor  
cells. A bivalent antibody was raised against PSMGFR (i.e., a  
single antibody having  
the ability to bind simultaneously to two MGFRs was produced). MUC I  
tumor cells  
(T47Ds) were exposed to this antibody, and cell proliferation  
was studied as a function  
of concentration of the antibody. A growth/response curve  
typical of a growth  
factor/receptor - antibody response was observed.  
Specifically, at concentration low  
enough that only a small portion of the cells were exposed to the  
antibody, cell -  
proliferation was low. At a concentration of antibody high  
enough that one antibody  
could bind adjacent MGFRs, cell proliferation was maximized. At a high  
excess of  
antibody, each antibody bound only a single MGFR,  
rather than dimerizing adjacent  
MGFRs, and proliferation was reduced.

T47D (HTB- 133) cells, a human breast cancer cell line that  
overexpresses  
MUC I, were cultured to 30% confluency. An antibody raised  
against the PSMGFR  
portion of the WC I receptor, i.e. an antibody to the MGFR  
(Zymed, San Francisco,  
California, USA), was added to cells at varying concentrations in a  
multi-well cell  
culture plate. As a negative control, a second set of T47D cells was  
treated with an  
irrelevant antibody (anti-streptavidin). Prior to adding  
antibody, cells were counted (at  
time zero). All experiments were performed in triplicate. Cells were  
allowed to grow in  
a CO2 incubator under. . . well) at 24 hours and again at 48 hours.  
Results, see Fig. 4, show that in a  
concentration-dependent manner, addition of antibody caused  
enhanced cell proliferation  
compared to the proliferation of the same cells treated with a control  
antibody. Figure 4  
is a graph in which measured cell growth at 24 and 48 hours is plotted  
as a function of  
anti-PSMGFR concentration. At the optimal antibody

concentration, when presumably one antibody binds bivalently to two MGFR portions of the WC I receptor, i.e.

In a similar experiment, a concentration of the anti-PSMGFR antibody, identified to maximize cell proliferation, was added to a first group of T47D tumor cells, grown as described above. The same amount of the anti-PSMGFR antibody was added to a set of control cells, K293 cells. Figure 5 shows that the addition of the anti-PSMGFR antibody to MUC I tumor cells (T47D) enhanced proliferation by 180% 24 hours, but had no effect on the control cells. The growth of the T47D cells plateaued to saturation, for cells with added antibody, at 48 hours. Control cells never reached saturation within the time frame of the experiment and were at 70% confluency at. . .

#### Activating Ligand Produced by MUCI-Presenting Cells Binds Multiple PSMGFRs

In this example, it is demonstrated that the activating ligand that triggers MUC I

tumor cell proliferation binds multiple PSMGFRs simultaneously. Colloid particles were produced that carry immobilized PSMGFRs, and suspensions of these colloids were

exposed to lysate and supernatants of (1) MUC1 tumor cells, or (2) control cells. MUC I

tumor cell lysates/supernatants caused the colloids to aggregate (suspension turns blue) because the activating ligand contained in them binds MGFRs on different. . .

Lysates and supernatants from four different tumor-associated cell lines (HTB- 1 3 3 (also called T47D), CRL- 1 500, CRL 1504 and CRL- 1 902; ATTC, American Type. . .

Rows E-H contained colloid particles carrying a random sequence peptide. Columns 2, 5, 8, and I I contained lysates from a tumor cell line that overexpresses NWC1 (HTB-133). Columns 3, 6, 9, and 12 contained lysates from a

tumor cell line that does not express WC 1 (CRL- 1 902). Columns 1, 4, 7, and 10 contain lysates from a tumor cell line that expresses, but does not overexpress, NWC I (CRL- 1 504). Columns 1-3: NTA concentration on colloid: 20 micromolar;. . .

absence (Fig. 10) of the protease inhibitor PMSF (phenyl methyl sulfonyl fluoride). Lysates from T47D cells were used because this breast tumor cell line was known to overexpress MUC I; additionally, the inventors presented evidence herein (see Fig. 8A-D) that this cell line. . .

Culture Collection, Manassas, VA) and are all breast carcinoma cell lines. Some lines have been shown to express or over express the tumor marker receptor MUC 1, Her2/neu or the oncogenic



enzyme cathepsin K.

from Mediatech supplemented with 1 mM sodium pyruvate, 10% FB S

Example 4b: Demonstration that the Ligand That Interacts with MUC 1 Cancer Cells

is a Multimer

In this example, it is demonstrated that a ligand produced by MUC1 cancer cells

that triggers cell proliferation in these cells is a multimer.

known as Metastasis Inhibition Factor NM23,

which has been implicated in both the promotion and inhibition of metastasis of human

15 cancers. Whether the role of NM23 is a tumor

suppressor or promoter may depend on the

type of cancer. In ovarian, colon and neuroblastoma

tumors, NM23 overexpression has

been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz R, Centeno

MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline ovarian

carcinoma, Anticancer Res, 1996; 16(3A): II 97-202). However, breast cancer studies

indicate that reduced expression of NM23 correlates with poor prognosis

(Mao H, Liu H,

Fu X, Fang Z, Abrams J, Worsham MJ, Loss of nm23 expression predicts distal

metastases and poorer survival for breast cancer, Int J Oncol

2001 Mar; 18(3):587-91).

from the protein gel band described in Figures

9 and 10 and that are derived from a protein implicated in many cancers called

Metastasis Inhibition Factor NM23 are shown below in Table 4. NM23

exists as a

hexamer and may recognize an unmodified form.

NOT

added to lysate) corresponded to more than one protein species, including 143, which

is a signaling protein implicated in many cancers, and

cathepsin D, which is a protease

and is also implicated in tumor progression. 143 exists as a

dimer and can

simultaneously bind to two, identical phospho-serine peptides. This

would dimerize the

MGFR portion.

QPGITFIAAK

3) human annexin V with Proline substitution by Threonine gi: 3212603

GLGTDEESILTLTSLR

DLLDDLKSELTGK

SEIDLFNIR

Examples 5a-d: Drug Studies Consistent with Mechanism Presented for MUC1 Cancer

In these examples, drugs that inhibit proliferation in MUC 1 tumor cells

specifically were compared to drugs that inhibit proliferation in both MUC1 tumor cells

20 and other cells. Drugs, both specific and non-specific, were

identified by exposing them

to PSMGFR-presenting colloids in the presence of WC 1 tumor

cell lysates. Drugs

were identified as those that prevented colloid-colloid interactions.

Cell studies resulted in a separation of these drugs into two groups - a group specific for MUC I tumor cells and a non-specific group. Non-specific drugs did not bind to PSMGFR, but are presumed to bind the activating ligand, and inhibit. . . somewhat toxic to both cell types, since they remove the activating ligand from interaction with the cells. Drugs specific for WC I tumor cells were found to bind to PSMGFR on beads, as demonstrated by HPLC analysis of the product of cleavage of PSMGFR. .

of the MUC I Receptor with its Activating Ligand(s)  
The following is an example of a working drug screening assay to identify anti-cancer agents. In this example, a histidine-tagged peptide derived from the portion of the MUC I receptor that remains attached to the. . .

The data below demonstrates the ability of anti-tumor drugs identified in accordance with the invention, specifically, calcimycin, fusaric acid, L-(X-methyl-dopa, butylindazone, NS 1 619 and etomoxir to inhibit proliferation of. . .

the interaction of the MGFR portion of the receptor with its activating ligands will block the proliferation of MUC I -presenting tumor cells. Therefore, drugs that were identified using the in-vitro drug screening assay described in Example 5a were tested. . .

compared. As seen in Fig. 13, Etomoxir, L-alpha-methyl DOPA, and Fusaric acid selectively inhibited proliferation of the NWC I - expressing tumor cells over K293 negative control cells. The DMSO control cells (both T47D and K293) show that DMSO alone does not effect cell proliferation. Fig. 13 is a histogram illustrating the selective inhibition of proliferation of tumor cells that aberrantly express the MUC I receptor (T47D cell line), in response to treatment with compounds of the invention, and lack. . .

that were shown in the functional cell proliferation assay (see Example 5b) to selectively inhibit the proliferation of WC I - presenting tumor cells by either directly binding to the MGFR portion or by acting on its modifying enzymes. Figure 15 is a bar graph that compares the percentage cell growth of WC I tumor cells (T47Ds) to a control cell line (K293 s), in response to treatment with novel drugs, (described in greater detail in. . .

provisional patent applications serial nos. 60/317,302 and 60/317,314, both filed on September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER). As is readily apparent, this group of drugs dramatically inhibited or completely prevented the proliferation of WC I -presenting tumor

cells, while leaving  
the control cells, in most cases, unaffected.

provisional patent  
applications serial nos. 60/317,302 and 60/317,314, both filed on  
September 5, 2001 and  
entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER) on  
cell  
growth for WC I -presenting cells (T47D) and a control cell line (K293).  
Notably, this  
group of drugs, which presumably. . .

6: Modulation of Inhibitory Effect of Etomoxir on Cell Proliferation  
Etomoxir, identified as a composition useful in treatment of NWC 1  
-dependant  
tumors in this invention, was shown to be specific for MGFR by  
modulating its effect on  
cell proliferation via competitive inhibition of. . .

Drugs That Affect MUC 1 Cleavage State  
The release of the MUC I IBR can be correlated to the progression of  
cancer.

Tumor derived cells expressing a cell surface receptor of the  
type described  
above, are cultured and treated with a drug candidate. Following. . .

Colloids bearing a binding peptide e.g. an antibody against a  
constant region of the  
receptor, remote from the enzyme cleavage site (amino acid 42 5 -479 for  
MUC 1;  
3o. . .

to the diagnostics and screening assays of the invention, the invention  
relates to therapeutic methods for the treatment and prevention of  
cancer and related  
products. For instance, in one aspect the invention relates to a method  
for treating a  
subject having a cancer or at risk of developing  
cancer by administering to the subject an  
agent that reduces cleavage of a cell surface receptor IBR from a cell  
surface receptor.

CLMEN 10 A method of treating a subject to reduce the risk of or progression  
of cancer  
comprising:  
administering to a subject who is known to be at risk for cancer  
or is diagnosed  
with cancer an agent for inhibiting interaction of an  
activating ligand with a portion of a  
cell surface receptor that interacts with the. . .

16 The method of claim 10, wherein the cancers is selected  
from the group  
consisting of. breast, prostate, lung ovarian, colorectal, and  
brain cancer.

31 A method of treating a subject to reduce the risk or of progression  
of cancer  
comprising:  
administering to a subject who is known to be at risk of cancer  
or is diagnosed  
with cancer, an agent for preventative clustering of portions  
of cell surface receptors  
that, interact with an activating ligand such as a growth factor. . .

36 The method of claim 31, wherein the cancer is selected from the group consisting of breast, prostate, lung ovarian, colorectal, and brain cancer.

84 A peptide species as in claim 68, wherein the fragment comprises at least a fragment of the sequence that corresponds to I that interacts with an activating ligand such as a growth factor to promote cell proliferation in association with MUC I -dependent tumorigenesis.

remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis such that a biomolecule that interacts with that portion of WC I that remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis interacts with the fragment.

in claim 109, wherein the synthetic drug is a derivative of etomoxir.

113. A method for treating a subject having a cancer characterized by the aberrant expression of MUC1, comprising:

administering to the subject ftisarinic acid in an amount effective to reduce tumor growth.

114. A method as in claim 113, wherein the subject is otherwise free of symptoms calling for treatment with calcimycin.

115. A method wherein levels of shed interchain binding region are reduced relative to a control sample.

119. A method for treating a subject having a cancer characterized by the aberrant expression of WC I, comprising:

administering to the subject etomoxir in an amount effective to reduce tumor growth.

120. A method as in claim 119, wherein the subject is otherwise free of symptoms calling for treatment with etomoxin

121. A method wherein levels of shed interchain binding region are reduced relative to a control sample.

125. A method for treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising:

administering to the subject L-(x-methyl-dopa in an amount effective to reduce tumor growth.

126. A method as in claim 125, wherein the subject is otherwise free of symptoms calling for treatment with L-(x-methyl-dopa.

127. A method wherein levels of shed interchain binding region are reduced relative to a control sample.

131. A method for treating a subject having a cancer characterized by the aberrant expression of WC 1, comprising:

administering to the subject calcimycin in an amount effective to reduce tumor growth.

132. A method as in claim 131, wherein the subject is otherwise free of symptoms calling for treatment with calcimycin.

133. A. . . levels of shed interchain binding region are reduced relative to a control sample.

137. A method for treating a subject having a cancer characterized by the aberrant expression of WC I, comprising:  
administering to the subject butylindazole in an amount effective to reduce tumor growth.

138. A method as in claim 137, wherein the subject is otherwise free of symptoms calling for treatment with butylindazole.

. A method. . . levels of shed interchain binding region are reduced relative to a control sample.

143. A method for treating a subject having a cancer characterized by the aberrant expression of MUC 1, comprising:  
administering to the subject NS 1619 in an amount effective to reduce tumor growth.

144. A method as in claim 143, wherein the subject is otherwise free of symptoms calling for treatment with NS 1619.

145. A. . . composition and the biomolecule; and determining disruption of the interaction by the candidate drug.

150. A method of treating a subject having cancer or at risk for developing cancer comprising:  
administering to the subject an agent that reduces cleavage of a cell surface receptor.

151. A method of treating a subject having cancer or at risk for developing cancer comprising:  
administering to the subject an agent that reduces cleavage of a cell surface receptor interchain binding region from the cell surface.

152. The. . . - corresponds to amino acids 1085 through 1109 of Genbank accession # PI5941, PID G547937).

156. The method of claim 150, wherein the cancer is selected from the group consisting of, breast, prostate, lung ovarian, colorectal, and brain cancer.

157. The method of claim 150, wherein the cancer is characterized by the aberrant expression of the WC I receptor.

158. A method comprising:  
determining an amount of cleavage of a cell surface receptor interchain binding region from a cell surface; and  
evaluating indication of cancer or potential for cancer based upon the determining step.

159. A method as in claim 158, wherein the cell surface receptor is MUCL

160. A method as in claim 158, comprising diagnosing cancer in a subject by  
determining an amount of shed cell surface receptor interchain binding region in a subject sample; and  
evaluating indication of cancer or potential for cancer based upon the determining

step.

161. A method as in claim 158, wherein the evaluating step comprises correlating the amount in a sample to an amount in a control as an indication of cancer or potential for cancer.

. A method as in claim 158, comprising:  
determining an amount of cell surface receptor interchain binding region at the surface of a cell from a subject; and  
evaluating indication of cancer or potential for cancer based upon the determining step.

163. The method of claim 158, wherein the interchain binding region comprises a contiguous amino acid sequence of. . . 160, wherein the sample is a proliferating cell line derived from a subject's cells.

. The method of claim 158, wherein the cancer is characterized by aberrant expression of MUC I.

171. The method of claim 158, wherein the amount of interchain binding region is determined. . . by a method selected from the group consisting of MALDI, western blotting, PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic cell sorting, fluorescence activated cell sorting, bead-based assays or an ELISA assay.

172. The method of claim 158, wherein the amount. . . method comprising:  
determining a site of cleavage of a cell surface receptor in a sample from a subject; and  
evaluating an indication of cancer or potential for cancer based upon the determining step.

176. The method of claim 175, wherein the cell surface receptor is MUC I.

177. The method of. . . blood.

180. The method of claim 175, wherein the sample is a tissue sample.

181. The method of claim 175, wherein the cancer is selected from the group consisting of. breast, prostate, lung, ovarian, colorectal, and brain cancer.

182. A method as in claim 175, wherein the cancer is characterized by the aberrant expression of WC I.

183. The method of claim 175, wherein the site of cleavage is determined. . . a method selected from the group consisting of MALDI, western blotting, PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic cell sorting, fluorescence activated cell sorting, bead-based assays or an ELISA assay.

184. The method of claim 175, wherein the. . . of claim 185, wherein the surface cell receptor is WC I.

187. A method of diagnosing a physiological state indicative of cancer or potential for

cancer, comprising determining a specific cleavage state of WC I distinguishable from a different cleavage state of WC1.

. A method comprising:

determining a. . . 188, comprising comparing the first amount to the second amount as an indication of progression of and/or effectiveness of treatment for cancer.

190. A method as in claim 188, comprising comparing the first amount to the second amount as an indication for administration of an agent for prevention of cancer.

191. A method as in claim 188, wherein the subject is undergoing treatment for cancer, the method comprising comparing the first amount to the second amount as an indication of effectiveness of the treatment.

192. A method as in claim 188, wherein the cell surface receptor is WC1.

193. The method. . . method of claim 188, wherein the sample is a tissue sample.

I 0 199. The method of claim 188, wherein the cancer is selected from the group consisting of. breast, prostate, lung, ovarian, colorectal, and brain cancer.

. . . by a method selected from the group consisting of MALDI, western blotting, PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic cell sorting, fluorescence activated cell sorting, bead-based assays or an ELISA assay.

202. The method of claim 188, wherein the amount. . .

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	14.60	23.28

STN INTERNATIONAL LOGOFF AT 14:43:49 ON 13 JUN 2006